Remarks

Applicants' claims 1-16, 21 and 22 are pending, but the Examiner has withdrawn claims 21 and 22 as reading on non-elected species. Accordingly claims 21-22 are cancelled without prejudice the prosecution of the subject matter contained therein in a continued application.

Applicants appreciate the Examiner's reconsideration of the Piskins reference and its recognition in Applicants' accepted IDS.

Claims 1 and 4 are amended to remove the term "high molecular weight," which the Examiner has found to be indefinite. Support for amendments to the claims can be found in the claims or the specification as originally filed. "Spontaneous self assembly of the vesicles is discussed at least at paragraph [0092], without the use of co-solvent at paragraph [0108]. Release of the encapsulant by "hydrolysis-driven membrane poration" is described at least at paragraphs [0258]-[0259]. Claim 6 is reorganized, but supported by the original claim. The linear relationship is supported by the Figures, especially Fig. 15, and by at least paragraphs [0026], [0241]-[0242] and [0252]. No new matter has been added.

Regarding Applicants' Rights to Benefit from the Effective Filing Date of USSN 09/460,605

The Examiner has raised maintained the issue regarding Applicants' claim to the benefit of the filing date of Application No. 09/460,605, now U.S. Patent No. 6,835,394. According to the Examiner, the present application does not have support for the claims because there is no specific mention of the elected species. Applicants' present application is a continuation-in-part, repeating some substantial portion of the earlier nonprovisional application filed December 14, 1999, and adds new matter not previously disclosed, the continuation-in-part is entitled to the benefit of the filing date of the earlier nonprovisional application (now U.S. Patent No. 6,835,394) in accordance with MPEP 210.08. Accordingly, support for the elected species of a PEO-butadiene block copolymer is found at Tables 1 and 2 (listing polymers of EO (which are PEO species) and PB (polybutadiene) which form the claimed "PEO-based block copolymer" as defined in present claim 1, and at least at the first 2 paragraphs of Example 2, beginning at col. 27, line 36 of U.S. Patent No. 6,835,394, describing the spontaneous formation of "polyethylene oxide- polybutadiene (PEO-PBD)" vesicles.

As such, Applicants' benefit of an earlier filing date claims priority over references cited by the Examiner, specifically Discher *et al., J. Phys. Chem. B.*, 2002, which was published 3 years after Applicants' priority date of December 14, 1999.

Response to the Rejection under 35 U.S.C. § 112, second paragraph

Claims 1 – 16 have been rejected as indefinite under 35 U.S.C. § 112, second paragraph. Although Applicants do not agree that the terms "high molecular weight in claims 1 or 4, or the "blending" step of claim 6 are indefinite, nevertheless, in an effort to move this application to allowance, Applicants have amended the claims in compliance with the Examiner's requirement.

Claim 6 is rejected for the term "increases" and when the increase occurs. The claim has now been reorganized to describe the effect on release of the encapsulant when the original mol % of the the at least one hydrolytically degradable block is adjusted in the blend ratio.

Thus, in light of the amendments to claim 1, 4 and 6, the rejection is now moot. And Applicants ask that the application be reconsidered, and the rejection under 35 U.S.C. § 112, second paragraph removed.

Response to the Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1–16 under 35 U.S.C. § 103(a) as being unpatentable over Piskin *et al.*, in view of Won *et al.*, and in further view of Discher *et al.* For the reasons stated above regarding the priority issue raised by the Examiner, Applicants respectfully assert that the 2002 Discher reference is not proper prior art with regard to Applicants' invention because the cited reference was published three years after the priority date of Applicants' present application. Thus, Discher cannot be used by the Examiner to support a rejection under § 103(a), and Applicants ask that it be withdrawn.

Nevertheless, in making the rejection, the Examiner states it would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to make a mixed micelle of PEG-PLA and PEG-PBD by blending the two in aqueous solution, thereby spontaneously forming (self-assembling), controlled release, polyethylene oxide (PEO)-based polymersome vesicles that encapsulate doxorubicin within the resulting micelle. The Examiner cites Piskin for teaching copolymer micelles made from PEG-PLA, but states that they would not be suitable for drug delivery. To bridge the gap between Piskin and Applicants' disclosed invention, the Examiner relies on Won and Discher, but Applicants traverse such a conclusion.

Even if combined, the cited references fail to teach or suggest Applicants' invention. Not only does Piskin not teach blending PEG-PLA with PEG-PBD to form micelles that are suitable for drug delivery, as pointed out by the Examiner, Piskin does not teach the formation of "self-assembling" bi-layer membranes - *i.e.*, polymersomes – as taught by Applicants. What Piskin actually teaches are micelles formed by transesterification of PLA with PEG, resulting in small, packed micelles with a PLA core and PEG outer shell. (See Piskin, page 361-362, which describe esterification and Figures 1 and 10 which show the resulting structure of the PLA-PEG micelles.)

In marked contrast, Applicants' polymersomes do not require esterification for assembly, but it is not necessary for Applicants to identify every post formulation process that is not part of their claimed invention. Polymersomes, as taught by Applicants, spontaneously, self-assemble into a closed membrane bi-layer in aqueous solution *without* the need for additional organic solvents or chemical processes – including transesterification. See, amended claim 1, stating in the body of the claim that PEO-based polymersomes self-assemble "without secondary chemical processing." Moreover, esterified micelles as taught by Piskin have a different membrane structure and different chemical properties than the synthetic copolymer polymersomes that spontaneously self-assemble into a membrane bi-layer, as expressly claimed by Applicants. The vesicles are defined in paragraph [0062], preparation of the polymersomes begins at paragraph [0086], and characterization of the polymersomes begins at paragraph [0101] and there is no suggestion of any post formulation chemical processing. In fact, no post assembly processing is ever described or suggested in Applicants' specification, and none can be assumed, particularly since Applicants' repeatedly emphasize that the resulting vesicles are free of organic chemicals or other contaminants that would necessarily remain from any secondary chemical processing.

Applicants polymersomes release encapsulated material through hydrolysis-driven poration of the membrane, which occurs locally within the membrane, as disclosed in Applicants' specification at paragraphs [0257], [0258]. See claim 1. Release of encapsulated material in Applicants' invention, therefore, is a direct result of blending in an appropriate ration, the selected diblock copolymers, such that the ratio of hydrophobic portion to hydrophilic portion of the polymersomes drives release kinetics. Thus, the mechanism for release, the structure, and the formulation and formation of the Piskin micelle are entirely different from Applicants' claimed method of forming a polymersome of selected component copolymers that

when blended provides a controlled rate of release of the at least one encapsulant contained therein.

Moreover, because the Piskin micelles undergo post formulation processing to effect transesterification, the process of formation produces micelles that are *structurally* and *functionally* different from Applicants' self-assembled, controlled release polymersomes that include no transforming secondary chemical processing. Nevertheless, the Examiner has turned to Won for teaching that PEG-PBD is useful in making micelles, and asserts that one skilled in the art would have sought to combine known materials for the same purpose, such as disclosed in Piskin. However, because Piskin has been shown above to provide micelles that require post formulation chemical transformation (transesterification), thereby producing micelles that are *structurally* and *functionally* different from Applicants' self-assembled, controlled release polymersomes, the addition of Won to Piskin does nothing to change the basic structure of the Piskin micelle.

The Won paper was an early disclosure of the vesicle research in the Discher laboratory. But it fails to describe Applicants' current polymersomes, and offers no suggestion that the blend ratio of the polymersome can be used to control release of the encapsulant by hydrolysis-driven poration of the hydrolysable membrane components of the blend. Thus, none of the critical elements of Applicants' claimed invention are added by the addition of Won to the cited Piskin reference. Consequently, neither Piskin nor Won, alone or in combination, could have or would have taught one of ordinary skill in the art, at the time of the invention, a method of preparing self-assembling, *controlled release* polymersomes in accordance with Applicants' invention. Even if combined, Piskin and Won fail to teach how to determine the appropriate blend ratio of hydrophilic copolymer to hydrophobic copolymer, and how to blend copolymers in aqueous solution to produce amphiphilic high molecular weight PEO-based polymersomes having a desired controlled release rate. Moreover, absent Applicants' own specification, a practitioner would not suspect or know why the expressly claimed step in Applicants' formulation for predetermining the blend ratio would be relevant to expressly controlling the release rates of an encapsulated material from the resulting polymersome.

The Examiner further relies on Discher for suggesting blending of PEG-PBD with another PEG-based diblock copolymer to make mixed micelles. Of course, as noted above, Discher is not a proper reference for prior art purposes and cannot be used in making the §103(a)

rejection. Nevertheless, even if Discher were properly applied as a reference, it does not provide the necessary teaching or suggestion to lead one skilled in the art to combine the teachings of Piskin and Won to arrive at Applicants' invention in a manner asserted by the Examiner.

Like the Won references, the cited Discher reference reported the early vesicle research in the Discher laboratory. But the cited reference fails to describe Applicants' that the blend ratio of the polymersome can be used to control release of the encapsulant by hydrolytic poration of the hydrolysable membrane components. Nowhere in Discher is a method of determining the appropriate blend of hydrolysable component and inert component to effect self-assembly of polymersomes that will provide hydrolytically controlled release kinetics of encapsulant, as taught by Applicants' claimed invention. Thus, none of the critical elements of Applicants' claimed invention are added by the addition of Discher to the cited Won and Piskin references. Consequently, Discher fails to bridge the gap between Piskin and Won, and combined the cited references could not lead one of ordinary skill in the art, at the time of the invention, a method of preparing self-assembling, *controlled release* polymersomes in accordance with Applicants' invention.

Accordingly, the cited references, alone or in any combination, fail to teach or suggest each and every element of Applicants' claimed invention as expressly taught by Applicants' claims 1 – 16. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

In view of the foregoing, Applicants assert that claims 1 – 16 are in condition for allowance. Prompt and favorable consideration to this Amendment and Reply is respectfully requested. Should the Examiner have any questions or comments regarding Applicants' amendments or response, the Examiner is asked to contact Applicants' undersigned representative at (215) 772-7550.

Respectfully submitted,

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